REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on March 22, 2002. Claim 56 has been cancelled herein without prejudice to prosecution in a continuation application. Claims 60-67 have been added. Claims 31, 50, 67, and 60-67 are pending. All claims have been rejected.

A clean version of the amended claims with instructions for entry pursuant to 37 C.F.R. §1.121(c)(1)(i) is included above. A marked-up version of the amended claims pursuant to 37 C.F.R. §1.121(c)(1)(ii) is attached as Appendix I.

This amendment is to expedite prosecution and should not be construed as acquiescence in any ground of rejection. Applicants reserve the right to prosecute the originally filed claims in the future. The comments in the Office action are now addressed in turn.

Rejections under 35 U.S.C. § 112

Second Paragraph

Claims 31, 50, 51, and 56 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, Claim 31 is said to recite variables which do not bear any relationship to the claimed compounds. These variables relate to the deleted formulae and as such, have been deleted herein as well. Applicants believe that the Examiner's concerns have been addressed. Applicants request that the rejection be withdrawn.

First Paragraph

Claims 31, 5 0, 51, and 56 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the preparation of the claimed compounds, allegedly does not reasonably provide enablement for the use of the compounds. The Office further argues that the specification does not enable any person skilled in the art to use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

Accompanying the present amendment is a Declaration by Dr. Gustave Bergnes, one of the co-inventors of the subject application. Additional details on the activity of quinazolinone compounds are presented in such Declaration.

Compounds representative of the genus of the claimed compounds were subjected to the in vitro tests as reported in the Bergnes Declaration. Dr. Bergnes concluded from these studies that the compounds encompassed by the present claims "that a skilled person in the field would understand that the above compounds as well as others encompassed by the present claims

should have the effect of inhibiting KSP activity and be useful in treating a disorder associated with KSP kinesin activity and/or cellular proliferative diseases."

These compounds fall with the scope of the claims, as amended herein, and thus, provide additional support of the therapeutic utility of the present invention.

The Federal Circuit has stated that in vitro testing may establish practical utility for a compound. *Cross v. Iizuka*, 224 U.S.P.Q. 739, 748 (Fed. Cir. 1985). Moreover, where the disclosed in vitro utility is supplemented by similar in vitro and in vivo pharmacological activity of structurally similar compounds, the court held that the in vitro utility is sufficient to comply with the utility requirement. The pharmacological activity from the disclosed in vitro tests need only reasonably correlate with the similar in vitro and in vivo pharmacological activity of the structurally similar compounds. A rigorous correlation is not necessary. *Cross* 224 U.S.P.Q. at 747.

In vitro assays for inhibition are described in the scientific literature and the Specifiication and are accepted as predictive of activity. In addition, as shown in the instant application, a correlation between in vitro KSP inhibition and in vivo inhibition of cellular proliferation in tumor cell lines has been demonstrated for quinazolinone compounds. Applicants therefore submit that one of skill in the art would consider the in vitro inhibition displayed by the compounds of the instant invention as predictive of in vivo activity in the treatment of cellular proliferation disorders or other disorders mediated by KSP.

Applicants respectfully submit that where the assertions of thereapeutic utility appear to be believable on their face and straight forward, and no reason or authority in variance thereto has been advanced, the disclosed utility must be accepted as accurate. *In re Bundy*, 209 U.S.P.Q. 18 (CCPA 1981). On the basis of Dr. Bergnes's Declaration and the rationale of *Cross v. Iizuka,* Applicants submit that the disclosed utility for the claimed compounds has been demonstrated. Applicants respectfully request that the rejection be withdrawn.

Double Patenting

Claims 31, 50, 51, and 56 have been provisionally rejected under the judicially created docitrine of obviousness-type double patenting as being unpatentable over claims 31, 5 0, 51, and 56 of copending Application No. 09/699,047. Applicants respectfully disagree as the compounds having the substituent –NH(R_4) were deleted from the claims in the '047 application. Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. §102(b)

Kazhevnikov

Claim 31 has been rejected under 35 U.S.C. §102(b) as being anticipated by Kazhevnikov et al. Chem. Abstracts 78:16128u ("Kazhevnikov"). The rejection is respectfully traversed as applied to the amended claims.

The present invention is directed to a novel class of compounds having a core quinazolinone structure that are modulators of mitotic kinesins, and more particularly, modulators of the mitotic kinesin KSP. Applicants have amended the claims herein to focus on a particularly preferred embodiment of the present invention, namely, the quinazolinone amides of formula 1(d). As is detailed in the Specification and the Declaration by Dr. Gustave Bergnes filed herewith, compounds within this class have been shown to inhibit cell proliferation with K_i values well within the range of anti-proliferative agents used in the clinic. These compounds can be used to inhibit human KSP; to treat diseases of proliferating cells; to develop inhibitors and modulators of KSP; and the like.

According to another preferred embodiment, the claimed compounds have been defined by quite specific substituents at the various R groups. More specifically, the claimed compounds have an R_4 group that is substituted benzyl, heterocyclyl and R_{16}-alkylene or is lower alkyl, cyclohexyl; phenyl substituted with hydroxy, lower alkoxy or lower alkyl; benzyl; heteroarylmethyl; heteroarylethyl; heteroarylpropyl and R_{16}-alkylene, wherein R_{16} is di(lower alkyl)amino, (lower alkyl)amino, amino, lower alkoxy, or N-heterocyclyl. In addition, the claims of the instant invention stipulate that the stereogenic center to which R_2 and $R_{2'}$ is attached has an R-configuration. In other words, R_2 cannot be the same as $R_{2'}$.

As repeatedly indicated by the courts, anticipation requires that all of the elements and limitations of the claim be found within a single prior art reference. There must be no difference between the claimed invention and the disclosure provided by the reference, as viewed by a person of ordinary skill in the field of the invention. (*Scripps Clinic & Research Fdtn. v. Genentech, Inc.*, 927 F.2d 1565, 1576 [Fed. Cir. 1991]). Furthermore, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. (*In re Royka*, 490 F.2d 981, 180 USPQ 580 [CCPA 1974]).

According to the nomenclature used in the present specification, Kazhevnikov is cited as describing compounds having R_1 as an aryl group; and R_2, $R_{2'}$, R_4, R_5, R_6, R_7, and R_8 as hydrogen. Kazhevnikov does not teach compounds having the substituent patterns claimed herein. For example, in the pending claims, R_4 cannot be hydrogen. Moreover, the cited art does not teach compounds wherein R_2 is not the same as $R_{2'}$.

Applicants submit that Kazhevnikov does not teach every element of the claims; therefore, that the invention, as claimed herein, is not anticipated by Kazhevnikov. Applicants respectfully request that the rejection be withdrawn.

Debnath

Claims 31 has been rejected as being anticipated by Debnath *et al.* (1999) J. Med. Chem. 42:3203-3209 ("Debnath"). Applicants respectfully disagree and traverse this rejection.

Debnath describes a compound labeled as ADS-J14, which isallegedly embraced in the claimed invention. According to the nomenclature used in the present specification, Compound ADS-J14 has the following substituents:

R_1	benzyl
R_2 / $R_{2"}$	one is hydrogen with the other being methyl
R_4	m-chlorophenyl
R_5-R_8	hydrogen

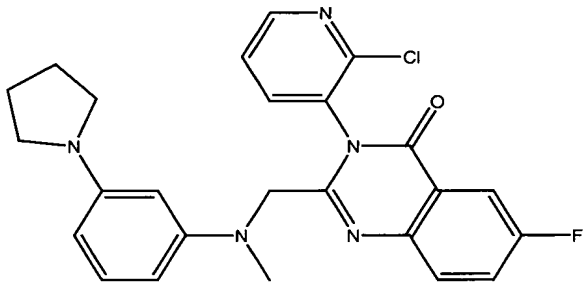
As described above, Applicants have discovered a class of compounds that show significant activity as kinesin inhibitors. As claimed herein, this class of compounds can be characterized, in part, by the specified R_4 groups. Specifically, in the claimed invention R_4 is substituted benzyl, heterocyclyl and R_{16}-alkylene or R_4 is lower alkyl, cyclohexyl; phenyl substituted with hydroxy, lower alkoxy or lower alkyl; benzyl; heteroarylmethyl; heteroarylethyl; heteroarylpropyl and R_{16}-alkylene, wherein R_{16} is di(lower alkyl)amino, (lower alkyl)amino, amino, lower alkoxy, or N-heterocyclyl. Thus, in contrast to the cited art, R_4 is not halogen substituted phenyl.

As such, the cited art does not anticipate the claimed invention. Applicants respectfully request that the rejection be withdrawn.

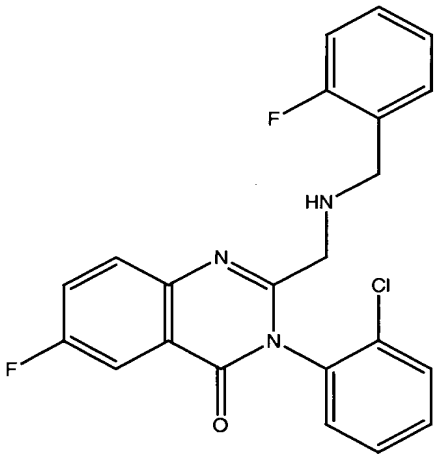
Chenard

Chenard et al. EP 884,310 or EP 900,568 ("Chenard") is cited as described quinazolinone compounds that are embraced by the claimed formula $-NHR_4$. Applicants respectfully disagree.

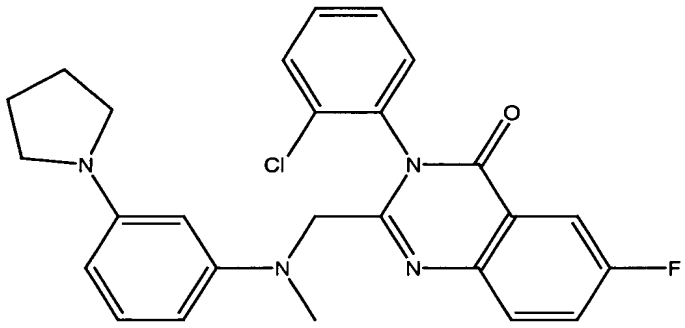
Chenard teaches a quinazolin-4-one core structure having a substituent of the formula -Y-Z-(BR^3R^4) wherein Y-Z can be either $-CH_2NH-$ or $-NHCH_2-$ and B is phenyl, pyridyl, or pyrmidyl. Example 8 of the '310 patent is drawn to:



Example 10 is drawn to:



Finally, Example 12 is drawn to:



As evidenced by the above structures, the compounds shown in Examples 8 and 12 of '310 patent, do not have a secondary amine side chain. Rather, they bear methyl substituents as well as substituted aryl groups. Moreover, as R_2 and $R_{2'}$ are both hydrogen, they are not attached

to a stereogenic center. As such, they do not anticipate the claimed invention which has a secondary amine side chain.

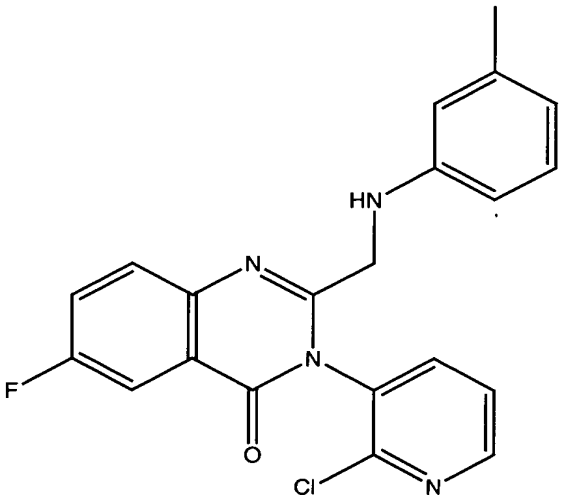
Likewise, the compound shown in Example 10 does not anticipate the claimed invention as R_4 in the Chenard compound is a halogen substituted phenyl. Again, as above, this compound does not comprise a stereogenic center attached to R_2 and $R_{2'}$. As discussed above with regard to Debnath, the claimed invention does not embrace this substituent pattern.

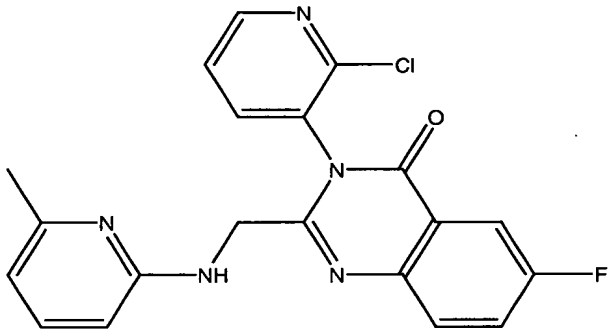
Chenard does not teach or suggest any quinazolinone amides of formula 1a, as claimed herein. More specifically, Chenard does not teach or suggest any quinazolinones having the specific substituent patterns claimed herein. Applicants submit that Chenard does not teach every element of the claims; therefore, that the invention, as claimed herein, is not anticipated by Chenard.

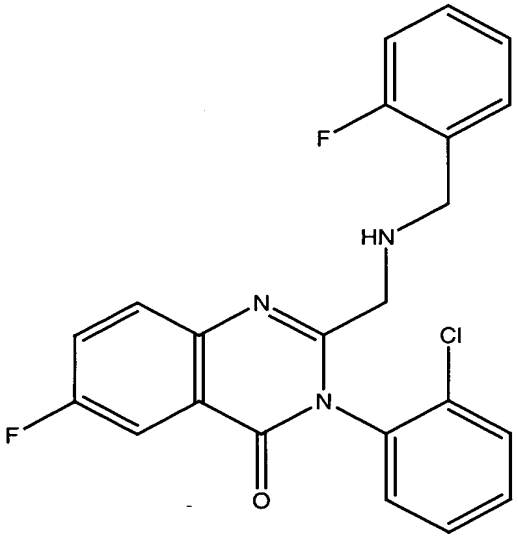
Rejections under 35 U.S.C. §102(e)

Claim 31 has also been rejected under 35 U.S.C. §102(e) as being anticipated by Chenard et al. U.S. Patent No. 6,136,812 ("Chenard '812"). Applicants respectfully disagree and traverse this rejection.

The Office has cited Chenard for its teaching of the compounds on lines 31-51 of Column 28. These compounds have the following structures:







As the Examiner will note, none of the above compounds has a stereogenic center at the carbon to which R_2 and $R_{2'}$ are attached. As such, the cited art does not anticipate the claimed invention.

Rejections under 35 U.S.C. § 103

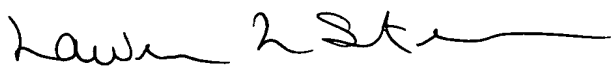
Claims 31 and 50 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chenard '310. Chenard is cited as above.

As discussed above, the claims have been amended herein to focus on a embodiment of the invention wherein the compounds have a stereogenic center and/or selected substituent patterns at R_1 or R_4. The cited reference does not teach or suggest these limitations. Applicants respectfully request that the rejection be withdrawn.

Conclusion

The Applicant respectfully maintains that all pending claims are in condition for allowance. Therefore, the Applicant respectfully requests a Notice of Allowance for this Application from the Examiner. Should any unresolved issues remain, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP

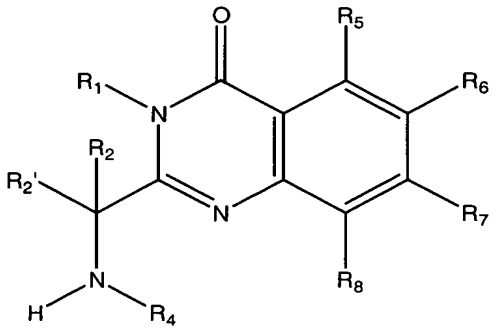


Lauren L. Stevens
Reg. No. 36,691

P.O. Box 778
Berkeley, CA 94704-0778

MARKED UP VERSION OF AMENDED CLAIMS

31. (Twice Amended) A compound having the following structure:



wherein:

R_1 is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl;

R_2 and R_2' are independently chosen from hydrogen, alkyl, oxaalkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl; or R_2 and R_2' taken together form a 3- to 7-membered ring;

[R_3 is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, substituted alkylheteroaryl, oxaalkyl, oxaalkylaryl, substituted oxaalkylaryl, R_{15}O- and R_{15}-NH-;

R_3' is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, substituted alkylheteroaryl and R_{15}-NH-;

R_3'' is chosen from alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl;

R_4 is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, substituted alkylheteroaryl, and R_{16}-alkylene-;]

R_4 is chosen from substituted benzyl, heterocyclyl and R_{16}-alkylene;

R_5, R_6, R_7 and R_8 are independently chosen from hydrogen, alkyl, alkoxy, halogen, fluoroalkyl, nitro, dialkylamino, alkylsulfonyl, alkylsulfonamido, sulfonamidoalkyl, sulfonamidoaryl, alkylthio, carboxyalkyl, carboxamido, aminocarbonyl, aryl and heteroaryl;

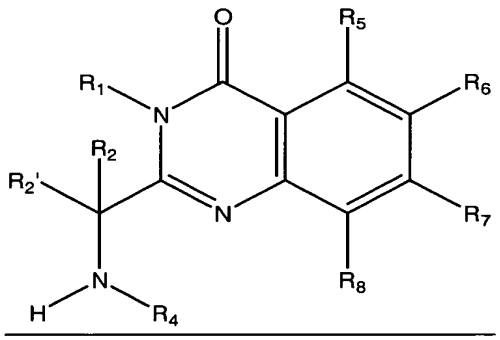
[R_{15} is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl;]

R_{16} is chosen from alkoxy, amino, alkylamino, dialkylamino, N-heterocyclyl and substituted N-heterocyclyl;

[with the proviso that when R_3 is R_{15}-NH- attached to carbonyl, both of R_2 and R_4 must be other than hydrogen]

wherein the stereogenic center to which R_2 and $R_{2'}$ are attached is of the R configuration, or a pharmaceutically acceptable salt thereof.

50. (Twice Amended) A compound having the following structure:



[according to claim 31] wherein:

R_1 is chosen from hydrogen, lower alkyl, substituted lower alkyl, benzyl, substituted

benzyl, phenyl, naphthyl and substituted phenyl;

R_2 is chosen from hydrogen, lower alkyl and substituted lower alkyl and R_2' is hydrogen; [and]

R_4 is chosen from lower alkyl, cyclohexyl; phenyl substituted with hydroxy, lower alkoxy or lower alkyl; benzyl; heteroarylmethyl; heteroarylethyl; heteroarylpropyl and R_{16}-alkylene, wherein R_{16} is di(lower alkyl)amino, (lower alkyl)amino, amino, lower alkoxy, or N-heterocyclyl**;**

R_5, R_6, R_7 and R_8 are independently chosen from hydrogen, alkyl, alkoxy, halogen, fluoroalkyl, nitro, dialkylamino, alkylsulfonyl, alkylsulfonamido, sulfonamidoalkyl, sulfonamidoaryl, alkylthio, carboxyalkyl, carboxamido, aminocarbonyl, aryl and heteroaryl;

wherein the stereogenic center to which R_2 and $R_{2'}$ are attached is of the R configuration,

or a pharmaceutically acceptable salt thereof.

51. (Twice amended) A compound according to claim 31 **or 50** wherein

R_1 is chosen from lower alkyl, benzyl, substituted benzyl and substituted phenyl;

R_2 is hydrogen or lower alkyl;

R_2' is hydrogen;

R_4 is R_{16}-alkylene-;

R_7 is hydrogen, fluoro, chloro or methyl;

R_5, R_6 and R_8 are hydrogen;

R_{16} is chosen from di(lower alkylamino), (lower alkyl)amino, amino, pyrrolidinyl, piperidinyl, imidazolyl and morpholinyl.